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Limitations to the use of carboplatin-based therapy in advanced ovarian cancer

Christina Fotopoulou*

Ovarian Cancer Action Research Centre and Imperial College, London

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ABSTRACT

Most patients with recurrent ovarian cancer (ROC) undergo a series of remissions and recurrences, therefore the additive or cumulative toxicity of chemotherapy must be factored into their treatment plan. There are challenges in defining tailored therapeutic approaches, including optimal timing and drug sequencing management strategies to treat patients with ROC. This is particularly relevant as new cytotoxic drugs and biological agents become available. Many of these drugs are associated with increased toxicity and with no observable survival advantage. Therefore current treatment options for the heavily-pretreated relapsing OC patient population are frequently guided by safety considerations and convenience. Rechallenge with platinum-based combination regimes is commonly limited by the risk of cumulative long-term toxicities. Not all patients can continue with platinum at second-line or, indeed, further relapses due to loss of activity or toxicity-related issues including hypersensitivity, neurotoxicity, alopecia and ototoxicity. In particular, hypersensitivity reactions are a concern and have been reported in approximately 15-20% of women receiving the drug. Trabectedin + PLD is a non-platinum combination that is well tolerated, with a manageable safety profile, which is independent of age.

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Factors influencing treatment decisions in this heavily-treated patient population in the UK

Decision-making strategies for optimal treatment of recurrent ovarian cancer (ROC) are complex as new cytotoxic drugs and an increasing number of biological agents become available. This presents challenges in defining the optimal timing and sequencing of the drugs or treatment regimen. A controversial issue of ROC treatment concerns the lack of an OS advantage observed with a number of investigational compounds and regimens, and they can be often associated with increased toxicity and no improvements in patients' QoL. Therefore, current treatment options for patients with ROC are frequently guided by safety considerations and convenience. A sub-analysis of the OVA-301 study showed that for platinum-

sensitive patients (PFI >6 months), median progression-free survival was 9.2 months with the trabectedin + PLD combination vs 7.5 months with PLD monotherapy (hazard ratio, 0.73; 95% CI, 0.56 to 0.95; $p=0.0170$). In fact, the median overall survival in the patient subgroup with a platinum-free interval in excess of 12 months (considered to have very PS disease) was 36.5 months with the combination, which was in the range of that obtained with platinum combinations [1].

Limitations to rechallenging with platinum-based therapy

Although therapeutic regimens that combine platinum-based therapy with other cytotoxic agents are the current standard

* Corresponding author: Address: Ovarian Cancer Action Research Centre and Imperial College, Du Cane Road, London W12 0NN, UK.

E-mail address: c.fotopoulou@imperial.ac.uk (C. Fotopoulou)

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of care for advanced ovarian cancer patients, the cumulative toxicities of cisplatin and carboplatin can present barriers for the long-term use of these agents [2,3]. As previously discussed, there are women with relapsing disease (particularly the PPS subgroup) who would benefit from a delay in platinum re-treatment to possibly enhance their response to platinum in a future application, or who are not ideal candidates for platinum-based therapy due to the toxicity profile of platinum or due to platinum-induced toxicity. There appear to be three main limitations to using carboplatin combinations, including allergy to carboplatin (hypersensitivity), renal toxicity, and ototoxicity.

Hypersensitivity reactions (HSRs) to carboplatin are a particular concern, and have been reported in approximately 15-20% of women [2]. Symptoms of carboplatin HSRs are highly variable and can be mistakenly attributed to other agents, particularly when they are used in combination. They include itching, rash, chest tightness, emesis, blood pressure changes and facial swelling. The onset of the carboplatin-associated HSR is also highly variable, occurring either as soon as the infusion starts or after it is completed. When expectations for a positive outcome with platinum are good, then desensitisation protocols may be useful to continue platinum-based therapy, and success rates in excess of 50% have been reported [2]. However, for example a 12-step desensitization protocol that administers the total dosage of carboplatin at increasing doses and faster rates over an extended period of time, requires adequate support in an intensive care unit or allergy department. All with the attendant burden on staffing and resources, and of course patient preference [1,2].

Other clinically significant sequelae such as neurotoxicity, severe cumulative myelosuppression, renal toxicity and ototoxicity are commonly caused by platinum-based chemotherapy. Indeed neurotoxicity, which influences patient's quality of life, is a dose-limiting adverse effect for all platinum compounds, and there is a high probability of persistent neurotoxicity including residual neuropathy (~20% of OC patients) associated with carboplatin plus paclitaxel treatment [4]. Carboplatin causes dose-limiting and cumulative myelosuppression, characterised by frequent and severe thrombocytopenia, granulocytopenia and anaemia. Likewise, cisplatin is associated with several cumulative and irreversible toxicities, including dose-dependent renal tubule toxicity and neurotoxicity [5]. Cumulative doxorubicin and paclitaxel exposure must also be monitored to minimize the risk of patient morbidity due to cardiotoxicity and neuropathy. Gemcitabine has many overlapping toxicities with other agents, and care must be taken with combination regimens to avoid synergy of these adverse effects [3].

Toxicity issues should be carefully taken into account before considering platinum re-treatment, as the platinum-associated cumulative and irreversible toxicities may jeopardise its long-term intervention on subsequent relapses. Consideration of platinum-induced cumulative toxicity takes on greater significance as the number of salvage regimens increase, as it can be given only to those patients for whom the toxicities would be acceptable. This underscores the need for alternative therapeutic options, including an efficacious non-platinum regimen with an acceptable toxicity profile.

Other factors that influence treatment decisions in this heavily-treated patient population have to be taken into account. For example, efficacy (clinical or symptom benefit), safety (specifically limitations with carboplatin due to hypersensitivity or residual toxicities) and QoL need to be

Box 1 – Main treatment-related adverse events reported in OVA-301 [1,8]

- Neutropenia - followed a predictable pattern of rapid onset and reversibility
- Most transaminase elevations improved to grade 1 or to pre-treatment levels within 15 days, and less than 2% of cycles had recovery times >25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time
- Trabectedin + PLD is less frequently associated with the toxicity profile shown with PLD monotherapy:
 - Hand-foot syndrome
 - Mucositis/stomatitis
- No detriment in QoL was observed adding trabectedin + PLD vs. PLD alone (all randomised patients)
 - Trabectedin + PLD had no decrement in patient-reported functional status and symptoms compared with PLD alone
 - Trabectedin + PLD is less frequently associated with alopecia, which can impact patients' QoL

considered. This could include health-related QoL, patient-reported outcomes regarding symptoms, and time without symptoms or toxicity. For example, although temporary in nature, alopecia is a visible reminder of cancer treatment and is extremely upsetting for many women. A recent pan-European survey into the QoL of 1743 patients with ovarian cancer by Oskay-Ozcelik et al. reported that alopecia was the single most troublesome side effect, with 42% patients reporting being bothered by alopecia [6]. It is known that platinum monotherapy and in combination with taxane does cause alopecia.

Furthermore, there is now an increasing body of evidence which shows that extending the platinum-free interval in relapsing patients with partially platinum sensitive ovarian cancer, also improves their response rate to platinum re-treatment at a later time point [7].

Trabectedin plus PLD is a non-platinum combination that is well tolerated with a manageable safety profile

Clinical evidence from OVA-301 shows that the toxicity related to the trabectedin + PLD combination was acceptable. The most common adverse events with the trabectedin + PLD combination were neutropenia and transient increased transaminase levels (Box 1 and Table 1). The results show that neutropenia followed a predictable pattern of rapid onset and reversibility and, similarly, transaminase increases appear early after administration (during treatment cycles one and two), then generally decrease in incidence and severity with subsequent treatment cycles (Fig. 1). Hence the clinician can assess the impact of the combination therapy on the patient from the first 2 cycles.

The impact of trabectedin plus PLD combination on patients' QoL

The impact of the trabectedin + PLD combination was also assessed on patients' QoL via QLQ-C30, a standardised QoL instrument developed by the EORTC to assess the quality

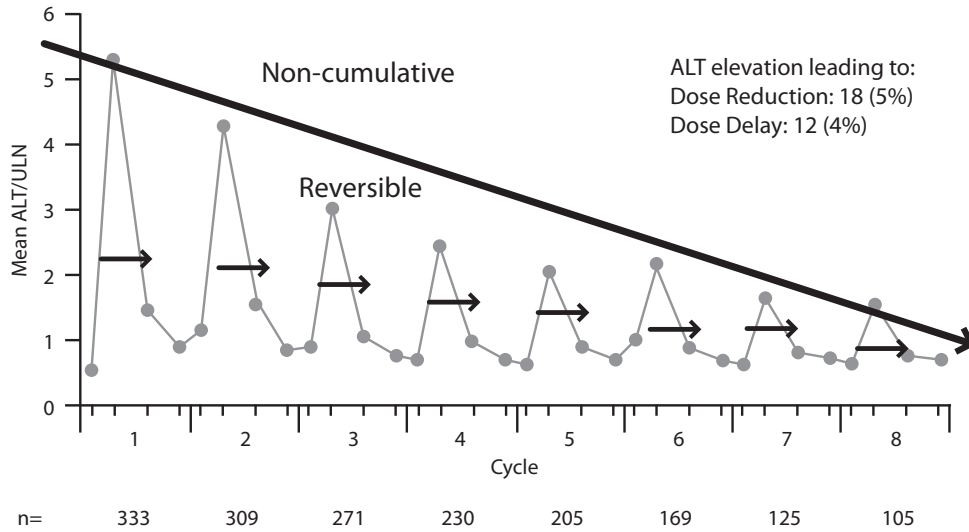


Fig. 1 – Mean transaminase levels (ALT) from all patients treated with trabectedin/PLD in OVA-301. The majority of elevations in transaminase levels were non-cumulative and reversible in OVA-301 [9]. Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved.

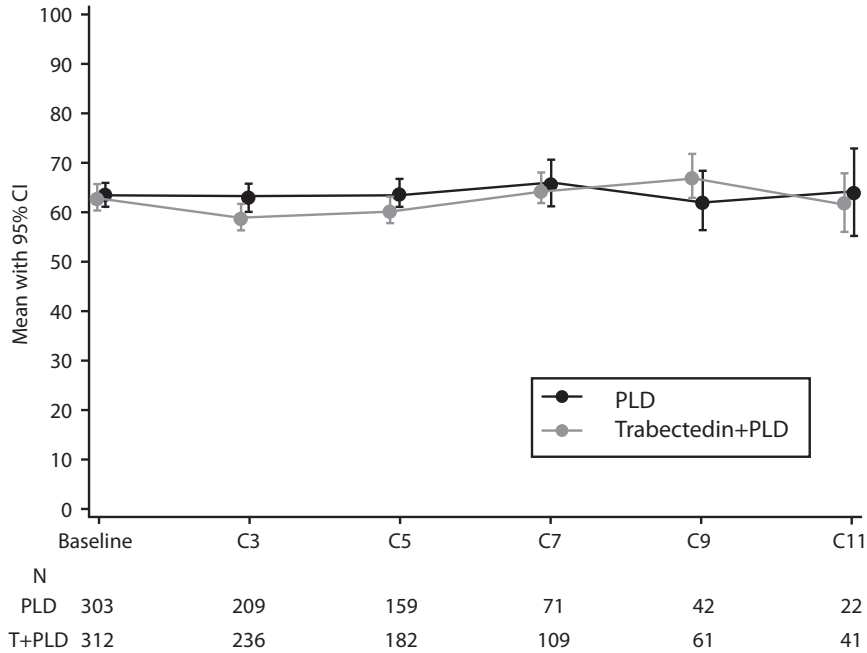


Fig. 2 – OVA-301: QLQ-C30 global health status scale, mean score over time in all randomised patients. There was no difference in QoL, assessed by QLQ-C30, between the 2 study arms in the overall study population [10]. Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved.

Table 1 – Selected grade 3-4 clinically relevant symptomatic AEs from OVA-301 [9]

	PLD n=330 (%)	Yondelis + PLD n=333 (%)
Hand-foot syndrome	20	4
Mucosal inflammation	6	2
Stomatitis	5	1

Trabectedin + PLD is well tolerated with a manageable safety profile, the most common serious adverse events are neutropenia and transient increased transaminases, which appear early and generally decrease in incidence and intensity over subsequent cycles.

of life of cancer patients. Results from OVA-301 showed no difference in patients' QoL between the 2 study arms (Fig. 2) [10].

Conclusions

During the course of their illness, patients with ovarian cancer may undergo multiple cycles of treatment, with alternating multiple episodes of remission and relapse. Therefore ROC patients are treated over a continuum in which therapeutic choices and strategies may impact the efficacy and safety of future therapies. Platinum rechallenge in combination or monotherapy regimes are often limited by hypersensitivity reactions and cumulative long-term toxicities, regardless

of the regimen. Desensitisation protocols may be useful so as to allow treatment to continue, albeit with significant burden on staffing and resources and with varying outcomes. The safety data from OVA-301 show that trabectedin + PLD can be considered as a treatment option at any relapse of ovarian cancer, including fully platinum-sensitive patients unsuited to receive subsequent platinum, with a manageable safety profile and equivalent efficacy. Therefore, trabectedin + PLD is a non-platinum alternative that is well tolerated. Furthermore, increasing evidence indicates that by extending the platinum-free interval with effective non-platinum agents such as trabectedin + PLD, patients are given some extra time to recover from any of the adverse effects of their prior platinum-based therapy with no detriment in QoL; and with even potential induction of their response to any subsequent platinum application, hence preserving their future treatment options.

Conflict of Interest Statement

Professor Fotopoulou received speaker fees from PharmaMar for her participation at the BGCS 2014 symposium. Professor Fotopoulou is responsible for the content of this article. Patricia Howard Associates received fees from PharmaMar to provide editorial assistance.

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